Meta-analysis of surgical strategies in perforated left colonic diverticulitis with generalized peritonitis

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Abstract: PURPOSE Surgical strategies for perforated diverticulitis (Hinchey stages III and IV) remain controversial. This systematic review aimed to compare the outcome of primary anastomosis, Hartmann procedure and laparoscopic lavage. METHODS A systematic literature search was conducted through Medline, Embase, Cochrane Central Register and Health Technology Assessment Database to identify randomized and non-randomized controlled trials involving patients with perforated left-sided colonic diverticulitis comparing different surgical strategies. The methodological quality of the included studies was assessed systematically (Grading of Recommendations, Assessment, Development and Evaluation) and a meta-analysis was performed. RESULTS After screening 4090 titles and abstracts published between 1958 and January 2018, 148 were selected for full text assessment. Sixteen trials (7 RCTs, 9 non-RCTs) with 1223 patients were included. Mortality rates were not significantly different between Hartmann procedure and primary anastomosis for Hinchey III and IV, neither in the meta-analysis of three RCTs (RR 2.03 (95% CI 0.79 to 5.25); p = 0.14, moderate quality of evidence) nor in the meta-analysis of six observational studies (RR 1.53 (95% CI 0.89 to 2.65); p = 0.13, very low quality of evidence). However, stoma reversal rates were significantly higher in the primary anastomosis group (RR 0.73 (95% CI 0.58 to 0.98); p = 0.008, moderate quality of evidence). Meta-analysis of four RCTs showed no significant difference between laparoscopic lavage for Hinchey III compared to sigmoid resection neither for mortality (RR 1.07 (95% CI 0.65 to 1.76); p = 0.79, moderate quality of evidence) nor for major complications (RR 0.86 (95% CI 0.69 to 1.08); p = 0.20, moderate quality of evidence). CONCLUSIONS This systematic review suggests similar rates of complications but higher rates of colonic restoration after primary anastomosis compared to Hartmann procedure in perforated diverticulitis with generalized peritonitis (Hinchey III and IV). Results in laparoscopic lavage for Hinchey III are not superior to primary resection. However, further studies with a careful interpretation of the meaning of re-interventions are required.

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Evaluation of Surgical Strategies in Perforated Left Colonic Diverticulitis with Generalized Peritonitis (Hinchey III/IV) – A Systematic Review and Meta-analysis

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Diverticulitis, perforation, Hartmann Procedure, Primary Anastomosis, Laparoscopic Lavage

Abbreviations:

ASA	American Society of Anesthesiologists
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HP	Hartmann Procedure
LL	Laparoscopic Lavage
LOS	Length of Hospital Stay
PA	Primary Anastomosis
RCT	Randomized Controlled Trial

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ABSTRACT

Background:

Surgical strategies for perforated diverticulitis (Hinchey Stage III and IV) remain controversial. This systematic review aimed to compare the outcome of primary anastomosis, Hartmann Procedure and laparoscopic lavage.

Methods:

A systematic literature search was conducted through Medline, Embase, Cochrane Central Register, Health Technology Assessment Database to identify randomized and non-randomized controlled trials involving patients with perforated left-sided colonic diverticulitis comparing different surgical strategies. The methodological quality of the included studies was assessed systematically (GRADE) and a meta-analysis was performed.

Results:

After screening 3396 titles and abstracts published between 1958 and October 2015, 138 were selected for full text assessment. Thirteen trials (5 RCTs, 8 non-RCTs) with 997 patients were included. Mortality rates were not significantly different between Hartmann Procedure and primary anastomosis neither in the meta-analysis of 2 RCTs (RR 2.09 (95% CI 0.66 to 6.65); p=0.454, moderate quality of evidence) nor in the meta-analysis of 6 observational studies (RR 1.53 (95% CI 0.89 to 2.65); p=0.987, very low quality of evidence). The stoma reversal rates were not significantly different after primary anastomosis compared to Hartmann Procedure (RR 0.77 (95% CI 0.51 to 1.17); p=0.106, low quality of evidence). Meta-analysis of 3 RCTs showed a trend to higher rate of major complications in laparoscopic lavage compared to sigmoid resection (RR 0.84 (95% CI 0.66 to 1.07); p=0.158, moderate quality of evidence).

Conclusion:

This systematic review suggests similar rates of complications as well as colonic restoration of primary anastomosis compared to Hartmann Procedure in perforated diverticulitis with generalized peritonitis. Recently published results regarding safety issues in laparoscopic lavage remain inconclusive and further investigation is needed.

INTRODUCTION

Diverticulosis of the colon is a common disease in western and industrialized civilizations. It occurs in up to 70% of patients older than 80 years of age[1, 2]. As many as 25% of patients with diverticular disease develop diverticulitis[3] and 10% - 20% of those who are hospitalized with acute diverticulitis require urgent surgical treatment[4]. In the case of diverticulitis, colonic perforation represents a dangerous complication with high morbidity and mortality rates of up to 50%[3, 5-7]. The severity of perforated diverticulitis is classified according to Hinchey[8]. While stage I and stage II are defined as covered perforation, stage III and stage IV represent free colonic perforations with generalized peritonitis, either purulent (III) or feculent (IV).

The acute management of perforated diverticulitis with generalized peritonitis (Hinchey Stage III and IV) has been a controversial topic over the past 50 years and a standardized therapeutic approach still does not exist. The Hartmann procedure (sigmoid resections with terminal colostomy and re-establishment of the colon continuity during a second operation) is a widely accepted standardized surgical approach. More recently primary anastomosis of the colon with or without diverting ileostomy[4, 7, 9, 10] has become an alternative in Hinchey III and IV peritonitis. A novel strategy to treat perforated colonic diverticulitis with purulent peritonitis (Hinchey III) is the laparoscopic lavage followed by delayed colonic resection in a second operation[11-13].

It is highly interesting to identify the best outcomes of the different strategies in terms of mortality and postoperative morbidity. Since previous reviews have had some limitations[14-16] and a substantial body of evidence comparing surgical approaches have recently became available, the aim of this systematic review was to compare the outcome of primary anastomosis vs. Hartmann Procedure as well as the impact of laparoscopic lavage in patients with perforated diverticulitis and generalized peritonitis.

METHODS

Selection criteria

Randomized controlled trials and non-randomized comparative studies comparing two surgical procedures in patients with perforated, left-sided colonic diverticulitis were selected. Hartmann Procedure, primary anastomosis (with and without protective stoma) and laparoscopic lavage (with and without suture of the perforation) were evaluated. Patients with colonic perforations due to causes other than diverticulitis (e.g. cancer, traumatic) were not considered.

In order to define a minimum quality standard, we only included studies containing at least 10 patients in each treatment arm. Studies were excluded in cases involving an obvious selection mechanism in non-randomized studies, which led to non-comparable patient groups such as age differences of more than 10 years between groups, a ratio of patients allocated to different treatments exceeding 4:1 or a ratio of higher ASA-Classification (≥3) exceeding 4:1.

The historic three-step approach (diversion by colostomy, followed by colonic resection and closure of the colostomy) was excluded due to strong evidence for superiority of primary resection[9]. Uncontrolled studies as well as case reports, description of surgical methods, studies on juvenile patients, abstracts, and surveys were excluded.
The primary endpoint of the present systematic review was all-cause mortality. Secondary outcomes were morbidity, stoma reversal rate and length of hospital stay (LOS). Complications were assessed according to the widely used Clavien-Dindo classification[17]. Complication grades IIIa-IVb were defined as major. Complications listed in studies published prior to 2004 were graded and categorized as major and minor using the Clavien-Dindo scale as a basis. *Search strategy*

A systematic literature search was carried out by an experienced information specialist from the Main Library of the University of Zurich (Medicine Careum) and comprised searches in MEDLINE (from 1966 to October 2015), EMBASE (from 1974 to October 2015),

The Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment Database (HTS). Search terms were defined. The function “related article” in PubMed was also used to identify articles. There were no restrictions on language or year of publication of the articles.

Study selection

The bibliographical details of all retrieved articles were stored in an Endnote file and duplicate records resulting from the various database searches were removed. Two reviewers (SS, TI) independently assessed titles and abstracts of all identified citations. The decisions of the two reviewers were recorded individually (select or reject) in the Endnote file and compared. Any disagreements were resolved by a third reviewer (SB). The two reviewers evaluated the full text of all potentially eligible papers and decided whether to include or exclude each study according to the inclusion and exclusion criteria. Any study that did not fulfil all of the criteria was excluded and its bibliographical details were recorded, with the reason for exclusion. Findings of the search process were illustrated according to the PRISMA[17] statement to provide the best possible clarity und transparency.

Data extraction

Two reviewers (SS, TI) independently recorded details about bibliography, study design, interventions, and patient outcome measures on a predefined form. A third reviewer (SB) resolved any discrepancies, if the two reviewers disagreed.

Risk of bias and quality assessment

An independent reviewer (CS) assessed the risk of bias in the included studies as high, low or unclear either using the Cochrane ’Risk of bias’ tool (Higgins 2011) or one of the following headings: 1. Random sequence generation. 2. Allocation concealment. 3. Control for confounding. 4. Blinding (performance bias and detection bias). 5. Incomplete outcome data (attrition bias). 6. Selective reporting (reporting bias). 7. Free of source of funding bias.

With regard to differences between surgical strategies, the quality of the evidence was assessed according to the grading of recommendations, assessment, development and evaluation (GRADE)[18-21], which considered the standard criteria risk of bias, heterogeneity, imprecision, indirectness and selective reporting.

Statistical analysis

For each study group, we calculated the risk for the outcomes (mortality and morbidity) and compared risks between groups using fixed effects meta-analysis in case of not statistical heterogeneity (I^2<40%) and random effects model in case of substantial statistical heterogeneity (I^2>40%). We reported relative risks and 95 per cent confidence intervals. Pooled estimates of mortality were calculated separately for RCTs and observational studies. We did not pool the data, if we deemed the studies to be too different in terms of their population, comparisons or study methods. The analyses were done using StataTM 12.1 (Stata Corporation, College Station, Texas, USA).

RESULTS

Study inclusion

Based on the literature search, 3396 studies published between 1958 and October 2015 were identified. After screening titles and abstracts, 138 articles were selected for full text assessment (Figure 1) with an agreement between reviewers (TI and SS) of 97.8 per cent. Thirteen studies with a total of 997 patients, published between 1990 and 2015, were finally included in the analysis. Eight studies compared Hartmann Procedure versus primary anastomosis[22-29], while five studies evaluated colonic resection (primary anastomosis or Hartmann Procedure) versus laparoscopic lavage[30-34]. Five of the selected studies were randomized controlled trials (RCTs)[22, 23, 31-33], while 8 were non-randomized, observational studies[24-30, 34] (Table 1 and 2).

Risk of Bias

The risks of bias of included studies are listed in Table 3a and 3b.

Hartmann Procedure versus Primary Anastomosis

The meta-analysis of RCTs (RR 2.09 (95% CI 0.66 to 6.65); p=0.454, moderate quality of evidence) and of observational studies (RR 1.53 (95% CI 0.89 to 2.65); p=0.987, very low quality of evidence) did not show statistically different risks for mortality (Figure 2, Table 4a und 4b). Based on the RCTs, major morbidity (RR 1.17 (95% CI 0.70 to 1.97); p=0.23, moderate quality of evidence) (Figure 3), as well as stoma reversal rates were similar for Hartmann Procedure and primary anastomosis (RR 0.77 (95% CI 0.51 to 1.17); p=0.106, low quality of evidence) (Figure 4). Missing data and extensive heterogeneity prevented a reasonable pooling of data on complications from non-randomized trials. Because of incompleteness of the data an isolated analysis for Hinchey III versus IV was not possible.

Laparoscopic lavage versus Hartmann Procedure or primary anastomosis

Both observational studies showed descriptively lower risks for morbidity for laparoscopic lavage (comparing with primary anastomosis[30] (RR 1.46 (CI 95% 0.72 to 2.95) or Hartmann Procedure[34] (RR 3.57 (95% CI 0.58 to 16.34)) (Figure 5). No relative risks could be calculated for mortality, as the number of deaths was too low to calculate meaningful mortality rates.

The meta-analysis of three RCTs showed a trend to higher risks for major morbidity in laparoscopic lavage compared with colonic resection (RR 0.84 (95% CI 0.66 to 1.07); p=0.158, moderate quality of evidence), while mortality rates were not significantly different (RR 1.07 (95% CI 0.61 to 1.88); p=0.82, moderate quality of evidence), (Table 4c, Figure 6 and 7).

DISCUSSION

Our systematic review shows that colonic resection with primary anastomosis shows similar mortality rates and stoma reversal rates compared to the Hartmann Procedure. Surprisingly, the results from recently published randomized controlled trials[31-33] demonstrate inferior outcome for laparoscopic lavage with regard to major morbidity and therefore raise several questions regarding safety.

Perforated left-sided diverticulitis with generalized peritonitis, Hinchey III and IV is a well-defined, life-threatening, clinical situation, which occurs frequently in every surgical emergency department. The wide range of therapeutic options include colonic resection without anastomosis (Hartmann Procedure)[35], colonic resection with primary anastomosis with or without diverting ileostomy[22] as well as laparoscopic lavage without resection of the inflamed colonic segment[11, 13]. However, scientific evidence for therapeutic decision-making is very limited. The vast majority of surgical literature reflects single cohort studies and retrospective studies as shown in previous systematic reviews[14-16]. Therefore, guidelines for clinical practice are primarily based on very low quality studies and expert opinion. The most recent guidelines of the American Society of Colon and Rectal Surgeons[36] recommend: "Following resection, the decision to restore bowel continuity must incorporate patient factors, intraoperative factors and surgeon's preference"**.** The present systematic review aimed to identify the current evidence of different treatment approaches in Hinchey III and IV patients. In contrast to previously published reviews, restrictive criteria for study inclusion were defined in order to minimize heterogeneity and to perform a reasonable pooling and meta-analysis of the data. Exclusively comparative trials without obvious selection bias between patient collectives (with regard to age, allocation and co-morbidities) were included. The meta-analysis focused on mortality as well as on major complications (Clavien Dindo IIIa-IVb).

Based on the described scientific search process (Figure 1) only 13 comparative trials could be identified, 5 randomized and 8 non-randomized trials (Table 1 and 2)**.** Risks for bias were lower in individual RCTs than in the observational studies (Table 3). The assessment of the quality of the evidence with regard to differences between surgical approaches was performed according to the widely accepted GRADE system[18-21]. While the quality of evidence of comparative results based on RCTs was moderate, analyses of observational trials only provide very low quality of evidence (Table 4). Meta-analysis by pooling estimates of specific outcome parameters such as mortality and major morbidity was performed in RCTs (Figure 2, 3, 6-7). Individual risk analyses of observational trials were carried out (Figure 2, 5). Due to heterogeneity or underreporting of data, no additional pooled analyses were performed neither to compare subgroups of patients such as Hinchey III or Hinchey IV nor to evaluate further outcome parameters such as hospital stay or costs in order to prevent misinterpretation.

Meta-analyses comparing Hartmann Procedure versus primary anastomosis from 2 RCTS did not show significant differences neither for mortality nor for morbidity (Figure 2 and 3). Both trials showed descriptively higher rates of stoma restoration after primary anastomosis. However, since numbers of patients were relatively small, pooled data of stoma reversal rates did not show a significant difference (Figure 4) either. It is noteworthy, that both RCTs had to be determined prematurely[22, 23]. Authors evaluated the conduction of RCTs comparing primary anastomosis with non-restorative colon resection for perforated diverticulitis as practically unfeasible because of a sophisticated allocation process in the emergency setting with low tolerance to perform alternative techniques based on a randomisation. Therefore, we are anxiously awaiting the results from the ongoing arm of the DIVA trial[22,23] comparing HP versus PA.

During the last decade, a minimal invasive approach utilizing laparoscopic lavage and drainage to particularly treat colonic perforation with purulent peritonitis (Hinchey III)

increased in popularity. Initial single cohort studies demonstrated very promising results, expanding the discussion by experts and within colorectal surgical societies about the best treatment of colonic perforation[11-13]. Our literature search revealed 5 comparative trials evaluating the impact of laparoscopic lavage compared with colonic resection (Hartmann Procedure or primary anastomosis), 3 RCTs [31-33] and 2 non-randomized trials[30, 34]. Both non-randomized studies individually showed very low mortality rates (0 and 1 death respectively) as well as a general trend towards lower morbidity rates in laparoscopic lavage (Figure 5)[30, 34]. With regard to the recently published RCTs, representing a lower risk of bias, they showed descriptively higher rates of major complications for laparoscopic lavage compared with sigmoid resection[31-33], (Figure 6).

However, a reliable interpretation of this data on LL might require a closer evaluation of the individual RCTs. On one side, the LOLA arm of the so called “ladies trial” (46 LL vs 40 sigmoidectomy) had to be stopped after interim analyses showed insufficiencies in regards to safety measures[33]. Major complication rates (mainly sepsis and intra-abdominal abscesses) of 35% in laparoscopic lavage (16/46) as compared to 18% (7/40) after sigmoid resection[33] were noted. On the other hand, mortality rates of all of the three RCTs were not significantly different. The SCANDIV trial[31] has the largest RCT (100 patients LL versus 98 patients colonic resection with or without anastomosis) showed a significantly higher re-intervention rate in the LL group (LL 20% versus 5,7% colonic resection p=0,01), while neither mortality nor severe complications after 90 days were significantly different. With regard to the DILALA trial[32] (39 LL versus 36 HP) short term results were similar in both groups.Subsequently, a conclusive interpretation of the value of LL in order to treat perforated non-feculent colonic perforation cannot be made based on the available data. The issue regarding re-intervention rate has become increasingly important and may be addressed by colorectal specialist. Is there a direct correlation between increased re-intervention rates and higher rates of severe complications or mortality? Can re-intervention be seen as an acceptable alternative with the

benefit of avoiding placement of an artificial stoma? This aspect may be part of the informed consent process with individual patients.
Hopefully long-term results of the ongoing randomized trials (Lap-LAND, DILALA) will provide further evidence with more definitive answers to these challenging questions.

This comparative analysis on different treatment options in cases of colonic perforation consists of the most sophisticated methodological search and evaluation of existing literature. Nevertheless, this systematic review also has limitations such as the inclusion of non-randomized trials. The described restriction of inclusion of studies based on methodological quality of individual trials minimizes bias and provides a high quality and reliable evaluation and interpretation of the current literature as compared with previously published reviews. As a second limitation, despite pooling of data, the number of included cases remains small, leading to less comprehensive findings.

To conclude, this systematic review suggests similar perioperative risks of primary anastomosis compared to Hartmann Procedure in perforated diverticulitis with generalized peritonitis (Hinchey lll/ lV). Preliminary results from recently emerged evidence addressing some safety issues regarding LL cannot be conclusively evaluated. More quality data needs to be collected and calculated.

FIGURES

Figure 7: Analysis of mortality of three randomized controlled trials comparing laparoscopic lavage with resection (res.) (Hartmann Procedure or primary anastomosis)

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